The goals of this review are two-fold: to examine the evidence in support of a role for insulin resistance and compensatory hyperinsulinemia in the pathogenesis of essential hypertension, and to evaluate the hypothesis that insulin resistance and its manifestations play major roles in the development of coronary heart disease in patients with essential hypertension. In both instances, only experimental results in human beings will be considered. Although it remains a scientific issue of great importance, the scope of this review precludes a discussion of the mechanistic link between insulin resistance/hyperinsulinemia and essential hypertension. (J Clin Hypertens. 2003;5:269–274) ©2003 Le Jacq Communications, Inc.

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as part of a routine health survey, and the normoten-
sive subjects were participants in the same survey,
selected to match the patients with respect to variables
such as sex, degree of obesity, ethnic background, type
of employment, and level of physical activity. Only
10% of the normotensive subjects had 2-hour plasma
insulin concentrations greater than 80 \( \mu \text{U/mL} \), com-
pared with 45% of the patients with hypertension. In
light of these and other findings, approximately 50% of
patients with hypertension can be considered to be
insulin resistant and hyperinsulinemic.

Based on the above considerations, it seems reason-
able to conclude that a substantial proportion of
patients with essential hypertension are resistant to
insulin-mediated glucose disposal and are hyperinsu-
linemic. In addition, they will tend to be somewhat glu-
cose intolerant, with elevated plasma triglyceride (TG)
and low high-density lipoprotein cholesterol (HDL-C)
concentrations as discussed subsequently. In other
words, hypertension in these patients exists as one of
the manifestations of the insulin resistance syndrome.

What Is Primary: Hypertension or Insulin
Resistance?

There are three lines of evidence providing sub-
stantial support of the view that insulin resist-
ance/hyperinsulinemia antedates hypertension.
1. Neither insulin resistance nor hyperinsulinemia are
increased in prevalence in patients with secondary
forms of hypertension.\(^{11,12}\)
2. Normotensive, first-degree relatives of patients
with high blood pressure who are at increased
risk to develop hypertension are relatively
insulin resistant and hyperinsulinemic when
compared with normotensive individuals with-
out a family history of hypertension.\(^{13–15}\)
Furthermore, these observations are independent
of differences in overall or regional adiposity.
3. Several prospective studies have shown that base-
line hyperinsulinemia, as a surrogate measure of
insulin resistance, predicts the development of
essential hypertension.\(^{16–20}\) Perhaps the publica-
tion that is the most relevant to the focus of this
review is the results observed in 1865 children
and adolescents followed over a 6-year period.\(^{19}\)
In addition to showing that the higher the fasting
insulin concentration at baseline, the greater the
increase in blood pressure over the 6-year period of
observation, evidence was presented that “high
insulin levels seem to precede the development of
a potentially atherogenic risk factor profile
including low HDL-C, high triglyceride, and ele-
vated systolic blood pressure.”

The evidence summarized to this point suggests
that insulin resistance and compensatory hyperinsu-
linemia are increased in prevalence in approximately
50% of individuals with hypertension, and the pres-
ence of these abnormalities in normotensive individu-
als predicts the eventual development of essential
hypertension. Furthermore, there is no evidence that
the decrease in insulin-mediated glucose disposal and
increase in plasma insulin concentration described in
patients with essential hypertension is secondary to
high blood pressure, per se.
INSULIN RESISTANCE, ESSENTIAL HYPERTENSION, AND CORONARY HEART DISEASE

Although coronary heart disease (CHD) is the major cause of morbidity and mortality in patients with essential hypertension, not all hypertensive individuals are at equal risk. The following section presents evidence in support of the view that the subset of patients with hypertension at greatest CHD risk is those individuals who are also insulin resistant/hyperinsulinemic.

CHD Risk Factors in Insulin Resistant/Hyperinsulinemic Patients With Essential Hypertension

As discussed earlier, not all patients with essential hypertension are insulin resistant. As a consequence, the CHD risk factors associated with insulin resistance will vary significantly in patients with equal degrees of blood pressure elevation. The results in Figure 2 demonstrate how different two groups of patients with essential hypertension can be when the subjects with hypertension seen in Figure 1 were subdivided into hyperinsulinemic (insulin resistant) and normoinsulinemic (insulin sensitive) subgroups. As shown in Figure 2, the plasma insulin concentrations in response to an oral glucose challenge are much higher in the insulin-resistant group. This is not surprising, since the two groups were stratified based on this criterion. However, it is also clear from Figure 2 that plasma glucose concentrations in response to the oral glucose challenge were also significantly higher in the insulin-resistant patients with hypertension. Since insulin resistance, hyperinsulinemia, and glucose intolerance have all been predictive of increased CHD risk, their existence in a subset of patients with hypertension supports the view that not all patients with high blood pressure are at equal risk to develop CHD.

Insulin resistance and compensatory hyperinsulinemia are associated with a dyslipidemia characterized by a high plasma TG and low HDL-C concentration. The prevalence of both of these changes is increased in patients with essential hypertension, and the data in Table I illustrate that an atherogenic lipoprotein profile can be seen in normotensive first-degree relatives of hypertensives.

Table I. Mean (±SE) Plasma Lipid and Lipoprotein Concentrations in Normotensive Individuals as a Function of Family History of Hypertension

<table>
<thead>
<tr>
<th>VARIABLE (MMOL/L)</th>
<th>POSITIVE FAMILY HISTORY</th>
<th>NEGATIVE FAMILY HISTORY</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (C)</td>
<td>4.80±0.15</td>
<td>4.44±0.12</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>0.50±0.06</td>
<td>0.23±0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IDL-C</td>
<td>0.34±0.07</td>
<td>0.21±0.02</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.65±0.12</td>
<td>2.54±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.34±0.06</td>
<td>1.47±0.05</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>VLDL+IDL+LDL-C</td>
<td>3.47±0.14</td>
<td>3.00±0.11</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Ratio of C/HDL-C</td>
<td>3.84±0.18</td>
<td>3.09±0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride (TG)</td>
<td>1.15±0.07</td>
<td>0.76±0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL-TG</td>
<td>0.71±0.07</td>
<td>0.40±0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IDL-TG</td>
<td>0.14±0.02</td>
<td>0.10±0.01</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-TG</td>
<td>0.19±0.01</td>
<td>0.16±0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL-TG</td>
<td>0.11±0.01</td>
<td>0.09±0.01</td>
<td>&lt;0.06</td>
</tr>
</tbody>
</table>

VLDL=very-low-density lipoprotein; IDL=intermediate-density lipoprotein; LDL=low-density lipoprotein; HDL=high-density lipoprotein

Figure 2. Plasma insulin (left panel) and glucose (right panel) concentrations in response to a 75 g oral glucose challenge in hyperinsulinemic (insulin resistant □) and normoinsulinemic (insulin sensitive ●) patients with hypertension. Reprinted with permission from J Intern Med. 1992;231:233–240.
patients with high blood pressure. In addition to being highly correlated with insulin resistance/hyperinsulinemia, a high plasma TG and a low HDL-C concentration are also well recognized CHD risk factors. Of more direct relevance are the data in Table II indicating that asymptomatic patients with high blood pressure identified as demonstrating cardiac ischemia by Minnesota Code Criteria were insulin resistant, hyperinsulinemic, and dyslipidemic, with higher TG and lower HDL-C concentrations than well matched hypertensive patients whose electrocardiograms were considered normal. Finally, the relationship between the dyslipidemia characteristic of insulin resistance and CHD in patients with essential hypertension has been emphasized by recent reports from the Copenhagen Male Study demonstrating the power of a high TG and low HDL-C concentration in predicting myocardial infarction in this patient population. In the absence of measures of either insulin resistance or plasma insulin levels, these authors used the changes in lipid metabolism as markers of the insulin resistance syndrome. The results of their analysis revealed that CHD events in patients with essential hypertension varied dramatically as a function of their plasma concentration ratio of TG/HDL-C, being markedly accentuated in those whose concentration ratio was in the highest tertile (insulin resistance syndrome) and essentially unchanged in the insulin-sensitive patients in the lowest tertile of TG/HDL-C concentrations.

**Link Between Insulin Resistance and Endothelial Dysfunction in Patients With Essential Hypertension**

The first step in the process of atherogenesis is the binding of circulating mononuclear cells (MNCs) to the endothelium. The effect of hypertension on this process was evaluated by isolating MNCs from patients with hypertension and quantifying their binding to cultured endothelial cells. Using this approach we were able to demonstrate that MNCs isolated from patients with essential hypertension adhered with significantly (p<0.001) greater avidity to endothelium than did MNCs from a matched control group with normal blood pressure. However, the enhanced binding of MNCs isolated from patients with hypertension to endothelium appeared to be more closely related to the degree of insulin resistance than blood pressure, per se, and the relationship between insulin-mediated glucose disposal and MNC binding was highly correlated in both normotensive (r=0.86; p<0.001) and hypertensive (r=0.74; p<0.001) individuals.

The interaction between circulating MNCs and the endothelium is modulated by the activity of cellular adhesion molecules (CAMs) secreted by endothelial cells. CAMs can be identified in the circulation, and elevated plasma concentrations of CAMs have been noted in association with a variety of conditions associated with insulin resistance, including essential hypertension. To explore the possibility that the insulin resistance commonly seen in patients with hypertension was responsible for the increased plasma concentration of CAMs, we defined in a group of healthy volunteers the relationship between insulin-mediated glucose disposal and the plasma concentrations of three CAMs—E selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cellular adhesion molecule-1 (VCAM-1). The results demonstrated that statistically significant relationships existed between degree of insulin resistance and E selectin (r=0.47; p<0.001), ICAM-1 (r=0.47; p<0.001), and VCAM-1 (r=0.47; p<0.001). Furthermore, plasma concentration of MNC binding to cultured endothelium was significantly correlated with the plasma concentrations of E selectin (r=0.5; p<0.05), ICAM-1 (r=0.55; p<0.001), and VCAM-1 (r=0.5; p<0.001). Thus, it appears that the subset of patients with essential hypertension who are insulin resistant have an increase in the endothelial production of CAMs, thereby increasing the likelihood that circulating MNCs will bind to endothelium and initiate the process of atherogenesis.

**Table II. Mean (±SE) Lipid and Lipoprotein Concentrations in Hypertensive Subjects With and Without ECG Evidence of Ischemic Changes**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>CHOLESTEROL (MMOL/L)</th>
<th>LDL-C (MMOL/L)</th>
<th>HDL-C (MMOL/L)</th>
<th>CHOLESTEROL/ HDL-C (RATIO)</th>
<th>TRIGLYCERIDE (MMOL/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=25)</td>
<td>5.05±0.24</td>
<td>3.11±0.22</td>
<td>1.36±0.08</td>
<td>3.95±0.31</td>
<td>1.16±0.12</td>
</tr>
<tr>
<td>Normal ECG</td>
<td>4.79±0.19</td>
<td>3.03±0.18</td>
<td>1.28±0.07</td>
<td>4.00±0.25</td>
<td>1.21±0.14</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>5.36±0.18</td>
<td>3.39±0.17</td>
<td>1.10±0.06*</td>
<td>5.04±0.23**</td>
<td>1.81±0.13**</td>
</tr>
</tbody>
</table>

ECG=electrocardiogram; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; *different from control (p<0.01); **different from control and normal ECG (p<0.02)
Another abnormality of endothelial function that may contribute to increased CHD risk in insulin-resistant individuals with hypertension is the dysregulation of asymmetric dimethylarginine (ADMA). ADMA is an endogenous inhibitor of nitric oxide synthase, recently shown to be elevated in patients with essential hypertension, which has also received considerable attention as an important CHD risk factor. Given this background, we thought it important to measure insulin-mediated glucose disposal, the plasma-insulin response to oral glucose, and plasma ADMA concentrations in normal volunteers and patients with essential hypertension. The results indicated that plasma ADMA concentrations and degree of insulin resistance were significantly correlated in both healthy volunteers \((r=0.73; p<0.001)\) and patients with essential hypertension \((r=0.70; p<0.003)\). Furthermore, plasma ADMA concentrations were similar in normotensive individuals and hypertensive patients when the two diagnostic groups were stratified into insulin-resistant or insulin-sensitive subgroups. Thus, as with the MNC binding and the plasma concentration of CAMs, the reported increase in plasma ADMA concentrations in patients with essential hypertension seems to be more a matter of insulin resistance than the increase in blood pressure.

**CONCLUSION**

Patients with high blood pressure, as a group, are insulin resistant, glucose intolerant, hyperinsulinemic, and dyslipidemic, with evidence of endothelial dysfunction. There is substantial evidence supporting the view that insulin resistance and/or compensatory hyperinsulinemia have a role in blood pressure regulation and may predispose a substantial number of individuals to develop high blood pressure. Of greater immediate clinical import is the fact that the abnormalities of glucose, insulin, lipid metabolism, and endothelial dysfunction that exist in substantial numbers of patients with high blood pressure seem to be a consequence of their insulin resistance. These insulin-resistance–associated changes are mainly responsible for the increased CHD morbidity and mortality that characterizes patients with essential hypertension. Given this information, it seems prudent to enlarge the scope of our therapeutic approach to patients with hypertension and to realize that blood pressure lowering is necessary, but not sufficient, if the goal is to reduce CHD in patients with essential hypertension. More succinctly, efforts at global CHD risk reduction must be implemented.

**REFERENCES**


